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A Randomized, Controlled, Multicenter Trial to Evaluate the Safety and Efficacy of Zotarolimus- Versus Paclitaxel-Eluting Stents in De Novo Occlusive Lesions in Coronary Arteries

The ZoMaxx I Trial

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Objectives A novel zotarolimus-eluting coronary stent system (ZoMaxx, Abbott Laboratories, Abbott Park, Illinois) was compared with a paclitaxel-eluting coronary stent (Taxus Express2) in a randomized trial of percutaneous intervention for de novo coronary artery stenosis. The primary end point was defined as noninferiority of in-segment late lumen loss after 9 months.

Background The ZoMaxx stent system elutes 10 μg/mm zotarolimus using a phosphorylcholine polymer loaded onto a novel stainless steel stent platform containing a 0.0007-inch inner layer of tantalum.

Methods Twenty-nine investigative sites in Europe, Australia, and New Zealand enrolled 401 patients, 396 of whom received a study stent.

Results After 9 months, late lumen loss was significantly greater in the ZoMaxx group (in-stent 0.67 $\pm$ 0.57 mm vs. 0.45 $\pm$ 0.48 mm; $p < 0.001$; in-segment 0.43 $\pm$ 0.60 mm vs. 0.25 $\pm$ 0. 45 mm; $p = 0.003$), resulting in significantly higher rates of >50% angiographic restenosis (in-stent 12.9% vs. 5.7%; $p = 0.03$; in-segment 16.5% vs. 6.9%; $p = 0.007$). The upper bound of the 95% confidence interval on the difference in in-segment late lumen loss between the 2 treatment groups (0.27 mm) exceeded the 0.25 mm value pre-specified for noninferiority. There were no significant differences between ZoMaxx and Taxus-treated groups with respect to target lesion revascularization (8.0% vs. 4.1%; $p = 0.14$), major adverse cardiac events (12.6% vs. 9.6%; $p = 0.43$), or stent thrombosis (0.5% in both groups).

Conclusions After 9 months, the ZoMaxx stent showed less neointimal inhibition than the Taxus stent, as shown by higher in-stent late loss and restenosis by qualitative coronary angiography. (J Am Coll Cardiol Intv 2008;1:524–32) © 2008 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) are intravascular metal scaffolds that are coated with antiproliferative agents designed to treat critical occlusive lesions of the coronary arteries. Stents eluting either sirolimus, paclitaxel, everolimus, or zotarolimus have each been shown to effectively inhibit restenosis in large-scale clinical trials (1–4). First introduced in 2001, DES have been widely applied, with over 6 million patients treated worldwide (5).

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The clinical trial reported herein was designed to compare the novel ZoMaxx zotarolimus-eluting stent (Abbott Laboratories, Abbott Park, Illinois) with the Taxus Express2 paclitaxel-eluting stent (Boston Scientific Corporation, Natick, Massachusetts). The ZoMaxx stent uses the TriMaxx (Abbott Laboratories) stainless steel–tantalum stent platform to deliver zotarolimus 10 μg/mm via a well-characterized polymer system based on phosphorylcholine (PC) (6). The objective of this randomized, prospective, multicenter trial was to show the safety and efficacy of the ZoMaxx stent system as compared with the Taxus Express2 stent system for patients with single de novo lesions in native coronary arteries using clinical, angiographic, and intravascular ultrasonic methods.

Methods

Study design and end points. The ZoMaxx I trial was a randomized, prospective, multicenter clinical trial conducted in accordance with the International Conference on Harmonization guidelines–Good Clinical Practices, Declaration of Helsinki, International Organization for Standardization 14155-1, International Organization for Standardization 14155-2, and Ethics Committee requirements. All patients gave written informed consent for participation.

Patients were considered eligible for inclusion if they complained of stable or unstable angina and/or had objective evidence of myocardial ischemia with angiographically proven single >50% lesions of 10 to 30 mm in length in 2.5- to 3.5-mm native coronary arteries. The major clinical exclusion criteria were acute myocardial infarction within the past 72 h, impaired left ventricular function with ejection fraction <30%, or lesions located within the left main coronary artery or within 2.0 mm of their ostia.

Secondary end points included device success (achievement of a final residual in-stent diameter stenosis of <30% using the assigned device only), lesion success (<30% residual stenosis using any percutaneous method), procedure success (lesion success without the occurrence of major adverse cardiac events [MACE]), angiographic rates of binary restenosis (≥50% diameter stenosis) after 9 months, neointimal hyperplasia volume after 9 months as measured by intravascular ultrasound (IVUS), and the 9-month incidences of ischemia-driven target lesion revascularization (TLR), ischemia-driven target vessel revascularization (TVR), and MACE (composite end point of non–Q-wave myocardial infarction [MI], Q-wave MI, TVR, and cardiac death). The first 250 randomized subjects with IVUS-eligible lesions were required to have IVUS evaluation during the procedure and at 9-month follow-up. A Q-wave MI was defined as the development of new pathological Q-waves in 2 or more contiguous leads with post-procedure creatine kinase (CK) or CK-MB levels elevated above normal. Non–Q-wave MI was defined as elevation of post-procedure CK levels to >2.0 times normal with elevated CK-MB in the absence of new pathological Q waves (World Health Organization definition). Acute luminal gain was defined as the difference between the minimum lumen diameter (MLD) at the completion of the stenting procedure and at baseline. Data are expressed as the mean ± SD for continuous variables and as frequencies for categorical variables (SAS Statistical Analysis Software for Windows, version 8.2, SAS Institute Inc., Cary, North Carolina).

Abbreviations and Acronyms

CK = creatine kinase
DES = drug-eluting stents
IVUS = intravascular ultrasound
MACE = major adverse cardiovascular events
MLD = minimum lumen diameter
PC = phosphorylcholine
TLR = target lesion revascularization
TVR = target vessel revascularization

Stent system. The ZoMaxx stent was designed to address the need for thin strut width and low profile, while maintaining radial strength and adequate visibility on fluoroscopy. The stent metal is a trilayer composite having 2 outer layers of 316L stainless steel and an inner layer of tantalum (Fig. 1) (7). The high atomic number of the 18-μm inner tantalum layer affords optimal radiopacity of the thin stent struts. The result is a DES with a strut thickness of only 0.0029 inches (74 μm), an important metric for minimizing arterial injury and restenosis (8–10).

The ZoMaxx stent elutes 10 μg/mm zotarolimus via a biocompatible PC polymer. Zotarolimus (Fig. 2) was specifically developed for use on intravascular stents and, like sirolimus, reversibly binds to FKBP-12, the cytosolic receptor of FK506 (11,12). Using this mechanism, zotarolimus inhibits the activation and proliferation of a variety mammalian cells at very low concentrations. Its potency for inhibition of human lymphocytes in vitro has been shown, as well as the reduction of inflammation in animal models of arthritis and encephalomyelitis (13). In cultured vascular cells, zotarolimus inhibits proliferation of canine and human smooth muscle and endothelial cells with IC_{50} in the low nanomolar range (11,12,14). It has minimal effects on cellular migration in vitro, theoretically allowing re-

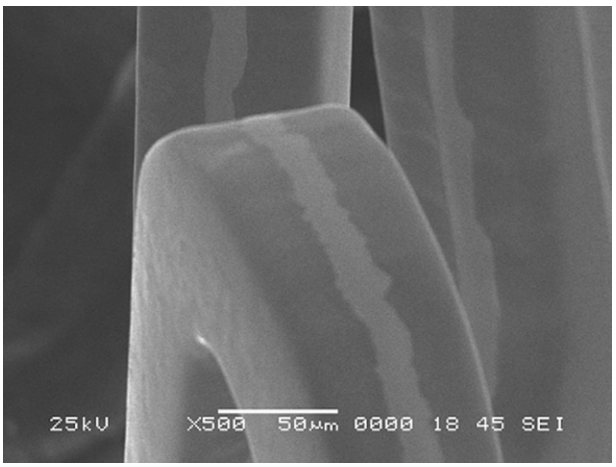

Figure 1. The ZoMaxx Stent Platform Consisting of a Trilayer of Stainless Steel, Tantalum, and Stainless Steel

endothelialization to proceed normally in the presence of the drug.

The phosphorylcholine polymer drug carrier on the ZoMaxx stent, known simply as PC-1036 or PC, is composed of the polymers 2-methacryloyloxyethyl phosphorylcholine (MPC), lauryl methacrylate (LMA), hydroxypropyl methacrylate (HPMA), and trimethoxysilylpropyl methacrylate (TSMA) in the molar ratios of MPC_{23}, LMA_{47}, $HPMA_{25}$, and $TSMA_5$ (6,15). It has been experimentally shown to have several properties improving blood–biomaterial compatibility, including minimal induction of fibrinogen absorption, platelet activation, platelet and erythrocyte adherence (15–17), inflammation, and neointimal hyperplasia (6,17–20). Phosphorylcholine has an extensive record of widespread clinical use and safety (6,21–23). It has also recently been shown to have considerable potential as a vehicle for drug elution, especially using highly lipophilic agents. It is formulated on the ZoMaxx stent to provide a measured rate of elution so that, in experimental animals, about 60% of the total zotarolimus dose is released during the first week, an additional 20% during the second week, and the remaining 20% over the next 2 weeks (24).

Treatment protocol. After patient eligibility was established and written consent obtained, the lesions were approached according to standard institutional interventional techniques. Patients received oral antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day) starting before the procedure and continuing for 6 months. After percutaneous access, heparin was administered to maintain an activated clotting time ≥250 s (or ≥200 s if glycoprotein IIb/IIIa antagonism was used). Diagnostic coronary angiography was performed in matched orthogonal views after nitroglycerin coronary injection (50 to 200 µg). After a 0.014-inch wire crossing of the target lesion, randomization (1:1 ZoMaxx vs. Taxus) was performed via an interactive telephone system.

Balloon pre-dilation of the target lesion was mandatory and was performed according to standard techniques ensuring that the length of the balloon was no greater than the intended stent length. Direct stenting was prohibited in this study. ZoMaxx stents were available in diameters of 2.5, 3.0, and 3.5 mm with lengths of 8, 18, 23, 28 mm (2.5-mm diameter only), and 33 mm (3.0- and 3.5-mm diameters only). Taxus stents were available in diameters of 2.5, 3.0, and 3.5 mm with lengths of 8, 12, 16, 20, 24, 28 mm (3.0- and 3.5-mm diameters only) and 32 mm (3.0- and 3.5-mm diameters only). Only 1 study stent was to be used per patient; however, additional stents could be implanted at the operator's discretion in the event of edge dissection or incomplete coverage.

Intravascular ultrasound images were acquired by motorized pullback at a constant speed of 0.5 mm/s. Baseline, post-procedure, and 9-month follow-up coronary cineangiographic images (Medis CMS, Leiden, the Netherlands) and IVUS tapes (TapeMeasure, Indec Systems, Inc., Mountain View, California) were analyzed using independent core laboratories (Brigham and Women's Hospital, Boston, Massachusetts, and Stanford University Medical Center, Palo Alto, California, respectively). Imaging studies performed within 284 days (9 months + 2 weeks) were included in the analysis.

Monitoring and statistical analysis. The study was monitored by independent contract research organizations (Hesperion AG, Allschwil, Switzerland, and Clinimetrics Research Associates, Inc., San Jose, California) and data were coordinated and analyzed by the Harvard Clinical Research Institute (Boston, Massachusetts). All MACE were re-

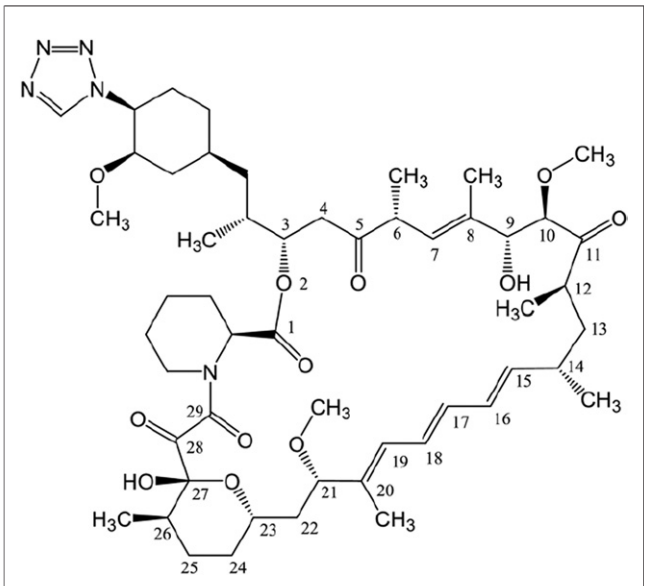

Figure 2. The Molecular Structure of Zotarolimus

viewed and adjudicated by an independent Clinical Events Committee whose members were unaware of treatment allocation. An independent Data and Safety Monitoring Board periodically reviewed blinded safety data.

The trial was designed to show noninferiority of in-segment late loss after 9 months (expected difference in means, μZoMaxx Stent − μTaxus Stent = 0), with a noninferiority margin of 0.25 mm and a standard deviation of 0.4 mm. Late luminal loss was defined as the difference between the MLD immediately after stenting and at follow-up. Because late loss values <0.6 mm for stented arteries between 2.5 and 3.5 mm in diameter have little clinical consequence, and the Taxus stent can be expected to generate 0.23 ± 0.44 mm in-segment late loss in this lesion cohort (2), a noninferiority margin of 0.25 mm was considered clinically and statistically appropriate. The trial was 99% powered to detect noninferiority with a 1-sided p value of 0.05.

Other treatment group comparisons were performed using the 2-sample *t* test for continuous variables, Fisher exact test for dichotomous variables, and Cochran-Mantel-Haenszel (Modified Ridit scores) for ordinal variables with more than 2 categories. Univariate and multivariate logistic regression was performed on the binary TVR results to understand the predictive value of several covariates. For the multivariate logistic regression, predictors were chosen by stepwise linear regression using an entry criteria of 0.2 and a stay criteria of 0.1.

Results

Four-hundred and one patients were enrolled sequentially in the study from 29 clinical sites in Europe, Australia, and New Zealand (Appendix). The first patient was enrolled on September 14, 2004, and the final patient was enrolled on July 18, 2005. Five patients (4 randomized to ZoMaxx and 1 randomized to Taxus) were subsequently deregistered after randomization and did not receive a study stent (3 were deemed to be ineligible after randomization, 1 sustained a complication before stent insertion, and 1 withdrew consent before stent insertion). This left a total of 396 patients for analysis (199 ZoMaxx and 197 Taxus).

The clinical and lesional demographics of the 2 patient cohorts are given in Table 1. The groups were fairly well matched demographically, as there were similar frequencies of diabetes (ZoMaxx 22% vs. Taxus 26%) and unstable angina (ZoMaxx 26% vs. Taxus 24%). However, there was statistically significantly more intervention in the right coronary artery in the Taxus group versus the ZoMaxx group (41% vs. 28%; p = 0.008). Furthermore, 8 lesions in the ZoMaxx group were ostial in location (within 2 mm of their origin); there were no ostial lesions in the Taxus group (4.0% vs. 0%; p = 0.0007).

Post-procedure metrics are given in Table 2. Lesion and device success were 99% for both stents (p = NS). There were no differences with respect to post-procedure in-stent or in-segment MLD, percent diameter stenosis, or acute gain between the 2 groups.

Table 1. Clinical and Lesional Demographics of Patients Enrolled in the ZoMaxx I Trial

	ZoMaxx (n = 199)	Taxus (n = 197)	p Value
Age (yrs)	63 ± 10	63 ± 11	NS
Male gender	75%	77%	NS
Diabetes	22%	26%	NS
IDDM	8.0%	8.6%	NS
Unstable angina	26%	24%	NS
Hypercholesterolemia	78%	72%	NS
Hypertension	69%	67%	NS
Family history of premature CAD	39%	34%	NS
Current smoker	24%	19%	NS
Prior MI	29%	29%	NS
Prior PCI	20%	25%	NS
Prior CABG	4.5%	1.0%	NS
LVEF	65% ± 12%	65% ± 11%	NS
Vessel location			0.025
LAD	48%	40%	
LCX	24%	19%	
RCA	28%	41%	*
Lesion location			0.031
Ostial	4.0%	0.0%	†
Proximal	39%	41%	
Mid	51%	51%	
Distal	6.0%	8.6%	
Lesion length (mm)	14.9 ± 5.7	14.6 ± 5.5	NS
RVD (mm)	2.79 ± 0.43	2.81 ± 0.46	NS
Total stent length (mm)	21.3 ± 5.9	20.8 ± 5.7	NS
Stent-to-lesion ratio	1.6 ± 0.6	1.6 ± 0.6	NS
Stents per patient	1.1 ± 0.4	1.1 ± 0.3	NS

*RCA vs. other locations, p = 0.008. †Ostial vs. other locations, p = 0.007.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; IDDM = insulin-dependent diabetes mellitus; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter.

Angiographic results are given in Table 3. Nine-month in-segment late lumen loss (primary end point) was 0.43 ± 0.60 mm and 0.25 ± 0.45 mm in the ZoMaxx and Taxus angiographic cohorts, respectively; the observed difference in the means was 0.18 mm. The distributions of in-segment late lumen loss in the ZoMaxx and Taxus groups are shown in Figure 3. Because the upper bound of a 95% confidence interval on the difference in the means (0.27 mm) was larger than the pre-specified noninferiority limit (0.25 mm), the primary angiographic end point of noninferiority of in-segment late lumen loss was not met. Consistent with the in-segment late loss results, in-segment binary restenosis was greater in the ZoMaxx group than in the Taxus group (16.5% vs. 6.9%; p = 0.007).

Table 2. Post-Procedural Results in the ZoMaxx I Trial

	ZoMaxx (n = 199)	Taxus (n = 197)	p Value
Lesion success	198 (99%)	195 (99%)	NS
Device success	197 (99%)	194 (99%)	NS
Procedure success	188 (95%)	189 (96%)	NS
In-stent	(n = 170)	(n = 175)	
MLD (mm)	2.71 ± 0.39	2.72 ± 0.43	NS
Diameter stenosis (%)	4.6 ± 7.9	4.4 ± 8.5	NS
Acute gain (mm)	1.90 ± 0.41	1.96 ± 0.49	NS
In-segment	(n = 170)	(n = 175)	
MLD (mm)	2.29 ± 0.47	2.29 ± 0.49	NS
Diameter stenosis (%)	20 ± 9.7	20 ± 9.5	NS
Acute gain (mm)	1.49 ± 0.45	1.53 ± 0.51	NS

MLD = minimum lumen diameter.

Similarly, in-stent late lumen loss was found to be statistically significantly greater after ZoMaxx stenting as compared with Taxus stenting (0.67 ± 0.57 mm vs. 0.45 ± 0. 48 mm; $p < 0.0001$), resulting in a higher frequency of in-stent restenosis in the ZoMaxx group (12.9% vs. 5.7%; $p = 0.025$). Even using nonparametric analysis, more appropriate for non-normal distributions such as late loss after implantation of DES (25,26), the difference in the medians remained statistically significant (median in-stent late loss ZoMaxx 0.58 mm vs. Taxus 0.41 mm; $p < 0.05$ using the Kruskal-Wallis test).

Clinical results at 9 months encompassing all follow-up angiography performed up to 284 days are given in Table 4; 9-month clinical follow-up was available in 96% of patients (382 of 396). There were no significant differences between treatment groups for any clinical end point. The rate of TLR was nearly double in the ZoMaxx group as compared with the Taxus group (8.0% vs. 4.1%), although the difference did not reach statistical significance (p = NS). There were no differences in the incidence of stent thrombosis whether protocol-defined (0.5% in both groups) or retrospectively applying the definitions suggested by the Academic Research Consortium (27) (1.0% in both groups).

Table 3. 9-Month Angiographic Results in the ZoMaxx I Trial

Angiographic Results	ZoMaxx (n = 170)	Taxus (n = 175)	p Value
In-stent			
MLD (mm)	2.03 ± 0.63	2.27 ± 0.58	<0.001
Diameter stenosis (%)	27 ± 21	19 ± 17	<0.001
Late loss (mm)	0.67 ± 0.57	0.45 ± 0.48	<0.001
Restenosis (%)	12.9	5.7	0.025
In-segment			
MLD (mm)	1.86 ± 0.59	2.04 ± 0.55	0.004
Diameter stenosis (%)	34 ± 19	28 ± 14	<0.001
Late loss (mm)	0.4 ± 0.60	0.25 ± 0.45	0.003
Restenosis (%)	16.5	6.9	0.007

MLD = minimum lumen diameter.

The IVUS results are given in Table 5. Neointimal volume obstruction by IVUS was statistically significantly greater after ZoMaxx stenting (14.6 ± 7.9% vs. 11.2 ± 9.6 %; $p < 0.018$). The incidence of late acquired malapposition was slightly less after ZoMaxx stenting, although the difference did not reach statistical significance (0% vs. 3%; p = NS).

To evaluate the possible predictive value of covariates in the ZoMaxx I study, both univariate and multivariable logistic regression analyses were performed on the entire patient cohort to identify significant risk factors for the need for follow-up TVR. The results, shown in Table 6, identify only ostial lesion location ($p = 0.002$) and the presence of diabetes ($p = 0.003$) as statistically significant predictors of the need for TVR after 9 months.

Discussion

Although a variety of antiproliferative agents have been suggested as putative inhibitors of stent-induced restenosis, only sirolimus (1), paclitaxel (2), everolimus (3), and zotarolimus (28) have been proven safe and effective in large-scale, multicenter, randomized clinical trials. One compound, zotarolimus (formerly known as ABT-578, Abbott Laboratories) (Fig. 2), has been specifically developed for use in DES having no other systemic formulation or indication. Intravascular stents that elute zotarolimus have been shown to be effective in inhibiting in-stent restenosis both in experimental animal models (29) and in patients undergoing percutaneous coronary intervention (4,28).

To date, 4 zotarolimus-eluting devices have been tested clinically: the Prefer (Abbott Laboratories) (30), Endeavor (Medtronic, Minneapolis, Minnesota), (4) ZoMaxx (31), and Resolute (Medtronic) (32) stents. The most extensively

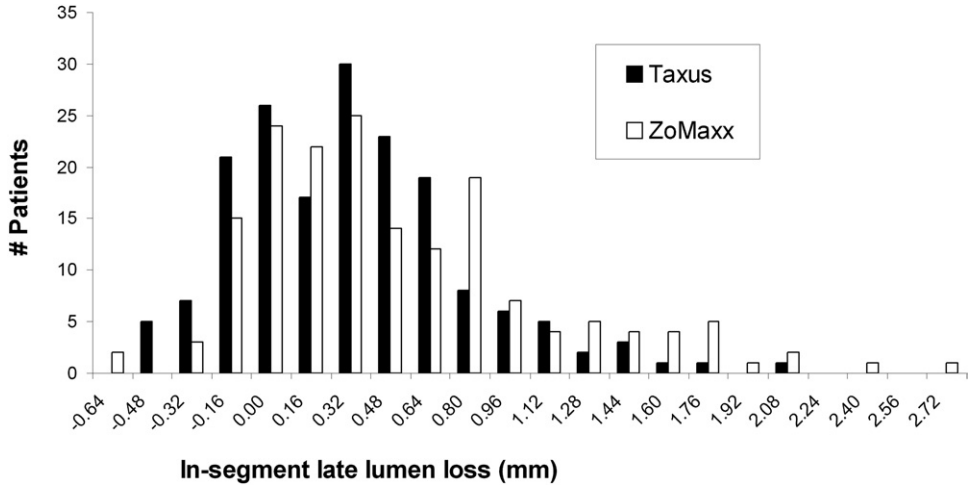

Figure 3. Distribution of In-Segment Late Loss in the Taxus and ZoMaxx Cohorts of the ZoMaxx I Trial

studied is the Endeavor stent, which also contains 10 μg/ml zotarolimus in a PC-based formulation that, in experimental animals, elutes approximately 95% of its drug load over about 15 days (4). The Endeavor II pivotal trial compared the Endeavor stent to the bare metal Driver stent in 1,200 patients, and the results showed highly statistically significant reductions in late lumen loss (in-stent 1.03 ± 0.58 mm vs. 0.61 ± 0.46 mm; $p < 0.0001$), angiographic binary restenosis (in-stent 33.5% vs. 9.4%; $p < 0.0001$), target vessel failure (15.1% vs. 7.9%; $p = 0.0001$) and MACE (14.4% vs. 7.3%; $p = 0.0001$) (28). Based on these and other clinical trial results (4,33,34), the Endeavor stent is now approved for clinical use worldwide.

The ZoMaxx stent was first tested clinically in the ZoMaxx IVUS trial, which enrolled 40 patients with symptomatic ischemic coronary occlusive disease at the Instituto Dante Pazzanese de Cardiologia in Saõ Paulo, Brazil (31). The lesion, procedure, and device-deployment success rates

Table 4. 9-Month Clinical Results in the ZoMaxx I Trial (Includes All Follow-Up Angiograms Performed Through 284 Days)

	ZoMaxx (n = 199)	Taxus (n = 197)	p Value
Q-wave MI	1.0%	0.5%	NS
Non–Q-wave MI	4.5%	4.1%	NS
TVR (ischemia-driven)	8.5%*	6.6%	NS
Cardiac death	0.0%	0.0%	NS
Total MACE†	12.6%	9.6%	NS
TLR	8.0%*	4.1%	NS
Non–TL TVR	2.5%	3.0%	NS
Target vessel failure	12.6%	9.6%	NS
All death	1.5%‡	0.0%	NS
Total stent thrombosis (protocol-defined)	0.5% (1)	0.5% (1)	NS
Acute stent thrombosis (24 h)	0.0%	0.0%	NS
Subacute stent thrombosis (1–30 days)	0.5% (1)	0.5% (1)	NS
Late stent thrombosis (>30 days)	0.0%	0.0%	NS
Total stent thrombosis (ARC-defined)	1.0% (2)	1.0% (2)	NS
Acute stent thrombosis (24 h)	0.5% (1)a	0.5% (1)b	NS
Subacute stent thrombosis (1–30 days)	0.0%	0.5% (1)a	NS
Late stent thrombosis (>30 days)	0.5% (1)c	0.0%	NS

*Includes 3 instances of TLR in ostial lesions. †MACE is a composite hierarchical end point of Q-wave MI, non–Q-wave MI, TVR, and cardiac death. ‡Three noncardiac deaths include 1 patient with acute renal and multiorgan failure at day 91, 1 patient with neuroendocrine malignancy at day 212, and 1 patient with intracerebral hemorrhage at day 274.

ARC = Academic Research Consortium (27); a = definite; b = probable; c = possible; MACE = major adverse cardiac events; TL = target lesion; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

Table 5. 9-Month IVUS Results in the ZoMaxx I Trial

	ZoMaxx (n = 114)	Taxus (n = 120)	p Value
Stent volume (mm^3)	155 ± 62	143 ± 58	NS
Lumen volume (mm^3)	132 ± 54	127 ± 55	NS
Neointimal volume (mm^3)	23 ± 16	16 ± 15	0.007
Neointimal volume obstruction (%)	14.6 ± 7.9	11.2 ± 9.6	0.018
Post-procedure SIA	19 (20%)	19 (19%)	NS
Persistent SIA	9 (9.6%)	10 (9.9%)	NS
Resolved SIA	10 (10.6%)	9 (8.9%)	NS
New (late-acquired) SIA	0 (0%)	3 (3.0%)	NS

IVUS = intravascular ultrasound; SIA = stent incomplete apposition.

were all 100% (40 of 40), and there was no MACE during the 4-month study. Follow-up angiography at 4 months showed in-stent and in-segment late lumen losses of 0.20 ± 0.35 mm and 0.17 ± 0.35 mm, respectively, with IVUS examinations showing a mean of 6.5 ± 6.2% neointimal volume obstruction. There were no instances of late acquired stent incomplete apposition or stent thrombosis. In comparison with a similar clinical trial using the nondrug TriMaxx stent studied angiographically at 6 months, the ZoMaxx stent significantly reduced in-stent restenosis from 25% to 2.7% (35).

These initial observations were extended through the ZoMaxx I clinical trial reported herein. The ZoMaxx I trial was designed to study a larger and more complex patient cohort with longer duration of follow-up in multinational geographies and to concurrently compare the outcome of ZoMaxx stent implantation with patients treated with the Taxus paclitaxel-eluting stent.

The ZoMaxx and Taxus patient groups in the ZoMaxx I trial were generally well-matched in both clinical and lesion characteristics. The exception was the preponderance of ostial lesions within the ZoMaxx cohort (n = 8) as compared with the Taxus cohort (n = 0). This occurrence was random and was uncovered as a result of retrospective core laboratory analysis of baseline angiograms, wherein lesions believed to be acceptable candidates for entry into the study were subsequently found to be within 2 mm of the artery's origin. It is known that percutaneous treatment of ostial occlusive lesions carries a substantially higher risk of restenosis (36–39), TVR (37), and 1-year mortality (40), and this is why patients with lesions that are located near one of the coronary ostia have been specifically excluded from pivotal clinical trials of DES (1,2,28). Indeed, the presence of an ostial lesion was the most significant multivariate predictor of TVR in the 386-patient cohort (p = 0.002), even slightly stronger than the presence of diabetes mellitus (p = 0.003).

The inclusion of patients with ostial lesions in the ZoMaxx group notwithstanding, there were no differences between the ZoMaxx and Taxus stent in device deployment or safety as shown by the high rates of device success (99% in both groups), a low stent thrombosis rate, and the absence of late stent thrombosis. There were no significant differences between treatment groups for any clinical metric that was evaluated (Table 4), although the study was not specifically powered to detect differences in infrequent events.

The most important finding in this clinical study was the statistically significant difference in late lumen loss between the 2 angiographic cohorts. The frequencies of both angiographic (87%) and IVUS (59%) follow-up are among the highest reported in any clinical trial of DES. After 9 months, patients treated with the ZoMaxx stent showed a mean in-segment late lumen loss of 0.43 ± 0.60 mm, whereas patients treated with the Taxus stent showed only 0.25 ± 0.45 mm of luminal loss (p < 0.001). Because the upper bound of a 95% confidence interval on the difference

Table 6. Univariate and Multivariate Logistic Regression Analysis of Predictors of TVR in the ZoMaxx I Trial

Predictor	Coefficient	SE	Odds Ratio	p Value
Univariate				
Diabetes	1.34	0.50	3.8	0.007
Lesion location (ostial vs. others)	2.11	0.86	8.3	0.014
Reference vessel diameter	−1.06	0.59	0.35	0.072
Degree of calcification (mod/severe)	−0.67	0.65	0.51	0.30
Lesion grade (C vs. all others)	−0.51	0.58	0.60	0.39
ZoMaxx vs. Taxus	0.36	0.50	1.44	0.47
Vessel location (LAD vs. others)	−0.11	0.50	0.90	0.83
Pre-procedure MLD	0.12	0.78	1.13	0.88
Lesion length	−0.002	0.04	1.0	0.96
Multivariate				
Lesion location (ostial vs. others)	2.77	0.91	16.0	0.002
Diabetes	1.61	0.54	5.0	0.003

LAD = left anterior descending coronary artery; MLD = minimum lumen diameter; TVR = target vessel revascularization.

between treatment groups for in-segment late loss was 0.27 mm (larger than the pre-specified 0.25 mm), the primary angiographic end point of noninferiority of in-segment late lumen loss was not met.

Given the differences in late lumen loss and the well-described curvilinear relationship of late loss to restenosis (25), it is not surprising that the ZoMaxx group was found to have statistically significantly higher rates of in-stent restenosis (12.9% vs. 5.7%; p = 0.025), as well as a trend toward increased ischemia-driven TLR as compared with Taxus (8.0% vs. 4.1%; p = NS). The specific mechanisms underlying these findings are speculative. The 2 stent systems differ in all critical design elements, including their stent platforms, drugs, pharmacological mechanisms of action, polymers, and formulations. The nondrug bare metal stent platforms seem to yield roughly comparable clinical and angiographic results, bearing in mind the relatively small patient cohorts subjected to rigorous angiographic follow-up (2,7,35). Both drugs have been shown to effectively inhibit mammalian cell proliferation in vitro and in animal models (29,41), and both have yielded variable clinical and angiographic results depending on their formulations, intervals of angiographic follow-up, and specific populations under study (range of in-stent late loss for paclitaxel-eluting stents: 0.30 to 0.81 mm [2,42–45]; zotarolimus-eluting stents: 0.12 to 0.67 mm [28,32,33,46]). It is noteworthy that the 9-month in-stent late lumen loss of patients treated with the ZoMaxx stent in this study (0.67 ± 0.57 mm) is strikingly similar to 8-month late lumen loss of patients treated with the Endeavor stent in each of Endeavor II (0.62 ± 0.46 mm) (28), Endeavor III (0.60 ± 0.48 mm) (33) and Endeavor IV (0.67 ± 0.49 mm) clinical trials (47). Thus, the prolonged release rate of ZoMaxx (24) as compared with Endeavor showed in nonconcurrent animal testing (4,24) had no apparent effect on results in humans. Interestingly, a zotarolimus-eluting stent using a different polymer formulation and having an even longer elution rate than ZoMaxx has recently been developed (Endeavor Resolute, Medtronic). Preliminary angiographic results in 30 patients suggest enhanced inhibition of neointimal hyperplasia using this formulation with a mean in-stent late loss of 0.12 ± 0.26 mm after 4 months (32). It can only be concluded that the efficacy of a given DES continues to be difficult to predict empirically and that long-term comparative clinical testing of each new formulation is required before its widespread application.

Conclusions

The ZoMaxx Coronary Stent can be safely implanted for the treatment of de novo coronary artery stenosis, as evidenced by the high rate of device implantation success (99%) and the low rates of subacute (0.5%) and late (0%) stent thrombosis. After 9 months, the ZoMaxx stent showed less neointimal inhibition than the Taxus stent, as demonstrated by higher in-stent late loss and restenosis by QCA and neointimal volume obstruction by IVUS.

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Key Words: drug-eluting stent ■ stent ■ zotarolimus ■ restenosis ■ coronary artery disease.

APPENDIX

For a complete list of investigators and institutions, please see the online version of this article.